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Comparison of neurokinin A and substance P on cardiovascular and airway function in man

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The airway and cardiovascular effects of intravenous neurokinin A (NKA) and substance P (SP) were compared in six normal subjects. Both SP and NKA increased skin temperature (SkT) and heart rate (HR), but SP was more potent than NKA by factors of 6 and 20 respectively. No change in systolic blood pressure (BP) occurred with either peptide, but diastolic BP fell significantly with SP infusion. SP caused bronchodilation and NKA bronchoconstriction. NKA and SP have differing physiological roles and may activate different receptor populations.

Keywords tachykinins substance P neurokinin A bronchoconstriction vasodilation

Introduction

The tachykinins are small peptides with a similar C-terminal sequence (Phe-x-Gly-Leu-Met.NH_2). Studies using a series of mammalian tachykinins have suggested the presence of distinct receptor subtypes (Iversen, 1985). Substance P(SP), an 11-amino acid peptide, contracts human airway smooth muscle *in vitro* (Karlsson & Persson, 1986) and when given intravenously to human subjects increases HR and SkT whilst causing diastolic BP to fall. Little effect on airway function is observed (Fuller *et al.*, 1987). Neurokinin A (NKA), coexists in sensory nerves with SP and appears to be the endogenous agonist of SP-E (or NK_2) receptors, whereas SP is the endogenous agonist of SP-P (or NK_2) receptors (Lee *et al.*, 1986). In animal and human airway smooth muscle NKA is more potent than SP *in vitro*, suggesting an NK_2 receptor (Karlsson & Persson, 1986). By contrast, SP appears to be the more potent vasodilator, suggesting that NK_1 receptors are present in systemic vascular smooth muscle (Hua *et al.*, 1984). In the present study we have compared the effects of infused NKA and SP on airway and cardiovascular function in man.

Methods

Six normal fasting volunteers (age range 23–40 years, five males) entered a randomized double-blind study separated by at least 48 h. Informed consent was obtained and the protocol was approved by the Brompton Hospital Ethics Committee.

Measurements

Heart rate (HR) was recorded from chest electrodes connected to a continous display electrocardiograph and blood pressure (BP) measured indirectly by automatically inflated sphymomanometer cuff. Skin temperature (SkT) was recorded by a thermistor placed on the left cheek. Airway function was measured by recording airflow at 30% of vital capacity from a forced partial expiratory flow manoeuver ($\dot{V}p30$) using a rolling seal spirometer connected to a microcomputer.

Protocol

An intravenous cannula was placed in a forearm

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vein with slow constant infusion of a gelatin plasma expander and measurements of all parameters made every 5 min during 20 min of control infusion, after which SP or NKA infusion was commenced (without the subjects knowledge) at 0.2 or 2.0 pmol kg^{-1} min^{-1} respectively for 5 min. Duplicate measurements of HR, BP, SkT and $\dot{V}p30$ were made at the second and fifth minutes of each infusion step. After 5 min the infusion rate was doubled unless there was a > 30 beats min^{-1} increase in HR or > 15 mm Hg fall in diastolic BP, until the highest infusion rate of 6.4 (for SP) or 64 pmol kg^{-1} min^{-1} (for NKA) was achieved. This was maintained for 20 min and then stopped after which recordings were made of all parameters at 2 and 5 min to ensure a satisfactory return to baseline levels.

Statistical analysis

Results are expressed in the text as mean ± standard error of mean (s. e. mean). Comparison between measurements taken at 2 and 5 min for all parameters at each dose for each peptide was made using Student's paired *t*-test to determine the time of maximal effect of each peptide. Statistical analysis was by two-way analysis of variance of each parameter and differences tested by Student's *t*-test with Bonferroni correction to allow for multiple comparisons. $P < 0.05$ was considered significant.

Results

All six subjects received an infusion of SP up to 3.2 pmol kg^{-1} min^{-1}, and two received 6.4 pmol kg^{-1} min^{-1}. All six subjects received NKA infusion up to 64 pmol kg^{-1} min^{-1}. Baseline values for all parameters are shown in Table 1. The maximal effect of both SP and NKA was at 2 min for all parameters and these values were used for statistical analysis. The results for all parameters are shown in Figure 1.

Table 1 Baseline values for heart rate, blood pressure, skin temperature and $\dot{V}p30$ prior to infusion of peptides in six normal human subjects: values shown are means ± s.e. mean ($n = 6$)

	Heart rate (*beats* min^{-1})	*Blood pressure (mmHg)* *systolic*	*diastolic*	*Skin temperature* (°C)	$\dot{V}p30$ (*l* min^{-1})
Mean	69.8	123.0	76.5	31.7	132.6
± s. e. mean	4.2	1.9	3.1	0.3	14.8

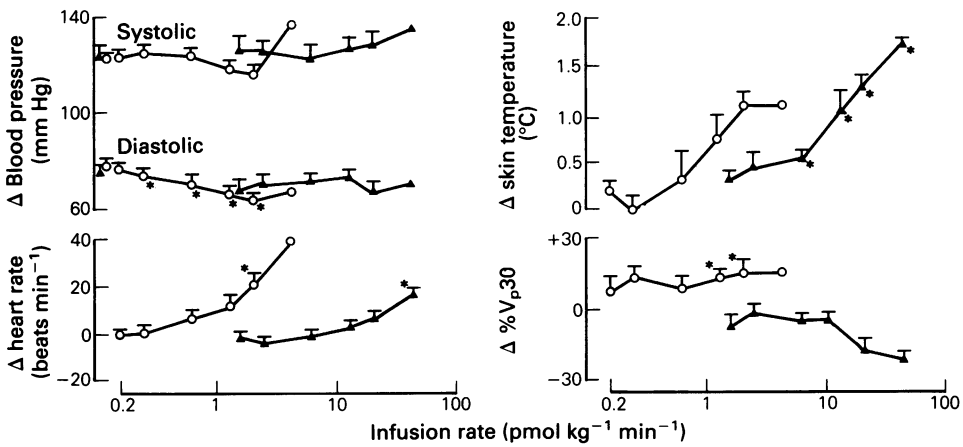

Figure 1 Change in heart rate, blood pressure, skin temperature and airflow at 30% of vital capacity from a partial flow volume manoeuvre ($\dot{V}p30$) with infusion of substance P (○) and neurokinin A (▲). Means ± s. e. mean ($n = 6$) are shown. Where no s.e. mean is shown the point is the mean of two readings. * indicates point significantly different from control ($P < 0.05$).

After an initial fall in HR with SP there was a dose-dependent rise to a maximum increment of 21 ± 5 beats min^{-1} at a dose of 3.2 pmol kg^{-1} min^{-1} ($P < 0.05$). HR rose with infusion of NKA to a maximum increment of 17 ± 2 beats min^{-1} at 64 pmol kg^{-1} min^{-1} ($P < 0.05$). The mean peptide concentration causing a 10 beats min^{-1} rise in HR was 1.52 pmol kg^{-1} min^{-1} for SP and 36.0 pmol kg^{-1} min^{-1} for NKA.

No significant change in systolic BP occurred with either peptide, and diastolic BP was unaffected by NKA. There was a dose-dependent fall in diastolic BP during SP infusion to a maximum decrement of 16 ± 4 mmHg at a dose of 3.2 pmol kg^{-1} min^{-1} ($P < 0.05$).

All subjects noted skin flushing at higher doses of each peptide. Skin temperature rose significantly in a dose-dependent fashion with both peptides; to a maximum increment of 1.12 ± 0.15°C at 3.2 pmol kg^{-1} min^{-1} ($P < 0.05$) with SP; and to 1.76 ± 0.2°C at 6.4 pmol kg^{-1} min^{-1} with NKA. The concentration causing a 1°C rise in skin temperature was 2.5 pmol kg^{-1} min^{-1} for SP and 16.0 pmol kg^{-1} min^{-1} for NKA.

$\dot{V}p30$ rose with increasing doses of SP to a maximum of 16 ± 5% above baseline at a dose of 3.2 pmol kg^{-1} min^{-1} ($P < 0.05$). In contrast, NKA infusion caused a progressive fall in $\dot{V}p30$ to 79 ± 4% of control values at a dose of 64 pmol kg^{-1} min^{-1} ($P < 0.05$).

Discussion

This study has confirmed our previous finding that infused SP causes a significant rise in SkT and HR accompanied by a fall in diastolic BP. $\dot{V}p30$ rose significantly at higher rates of infusion (Fuller *et al.*, 1987). By contrast, NKA was 20-fold less potent than SP in its effects on SkT and HR and resulted in bronchoconstriction, as indicated by a fall in $\dot{V}p30$. These results are in agreement with previous *in vitro* and *in vivo* animal studies. In guinea-pigs and rats both SP and NKA cause a dose related fall in mean arterial pressure with SP the more potent (Hancock & Hoover, 1985). Infused NKA cause increased insufflation pressures in guinea-pigs which may be due to bronchoconstriction or increased vascular permeability and consequent airway oedema (Hua *et al.*, 1984). As SP is a more potent mediator of increased microvascular leakage than NKA in airways and in human skin (Barnes *et al.*, 1986), and causes a fall in airway resistance after infusion, a direct effect on bronchial smooth muscle seems more likely. NKA is more potent than SP in causing contraction of human bronchial smooth muscle *in vitro* (Barnes, 1986; Karlsson & Persson, 1986).

Our study therefore supports the existence of multiple tachykinin receptors in man *in vivo*. The cardiovascular potency of SP is greater than that of NKA suggesting that NK_1 receptors mediate vasodilatation in the systemic circulation. In contrast, NKA causes bronchoconstriction whereas SP does not, suggesting that the tachykinin receptor in airway smooth muscle is an NK_2 receptor.

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